Synopsis

The thesis entitled "***Iodine and Copper Catalyzed Oxidative Cross Coupling Reactions: Design and Development of Carbon-Carbon and Carbon-Heteroatom Bond Forming Reactions***" is divided into two sections. Section-A, contains two chapters, describes the catalytic ability of iodine for cross coupling reactions. Section-B, divided into three chapters, presents the azidation of organic scaffolds under oxidative conditions.

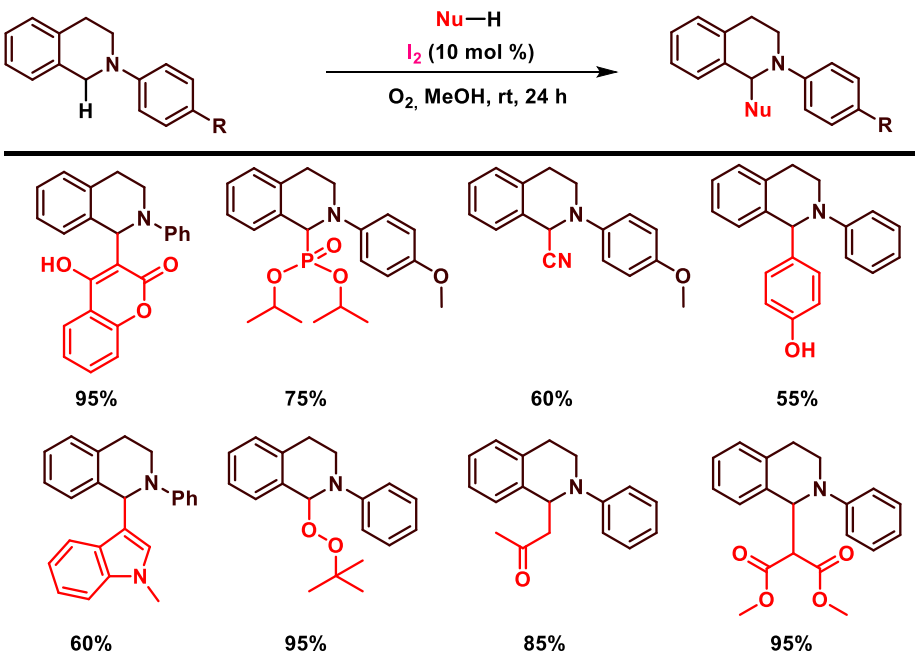
Section A

Chapter 1 presents a C-H functionalization of tetrahydroisoquinolines using iodine as a catalyst under aerobic conditions.[1] This methodology employs Cross Dehydrogenative Coupling (CDC) strategy as a key step, which is highly atom economical as it doesn't require pre-functionalized starting materials.[2] Owing to the importance of tetrahydroisoquinoline moiety which is present in the umpteen natural products, considerable attention has been put up to functionalize tetrahydroisoquinoline scaffold.[3] Iodine a non-metal which is non-toxic was found to catalyze the C-H functionalization of tetrahydroisoquinolines with a variety of nucleophiles such as coumarin, alkyl phosphite, phenols, indoles, acetone and dialkyl malonoates were coupled to it. Significant mechanistic study has been carried out to find the possible intermediate and support the mechanistic proposal. A few representative examples are highlighted in Scheme 1.[1]

[1] Dhineshkumar, J.; Lamani. M.; Alagiri, K.; Prabhu, K. R. *Org. Lett.* **2013**, *15*, 1092.

[2] Yeung C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215 and references cited therein.

[3] Dahlstrom, B.; Mellstrand, T.; Lofdahl, C. -G.; Johansson, M. *Eur. J. Clin. Pharmacol.* **1982**, *22*, 535.



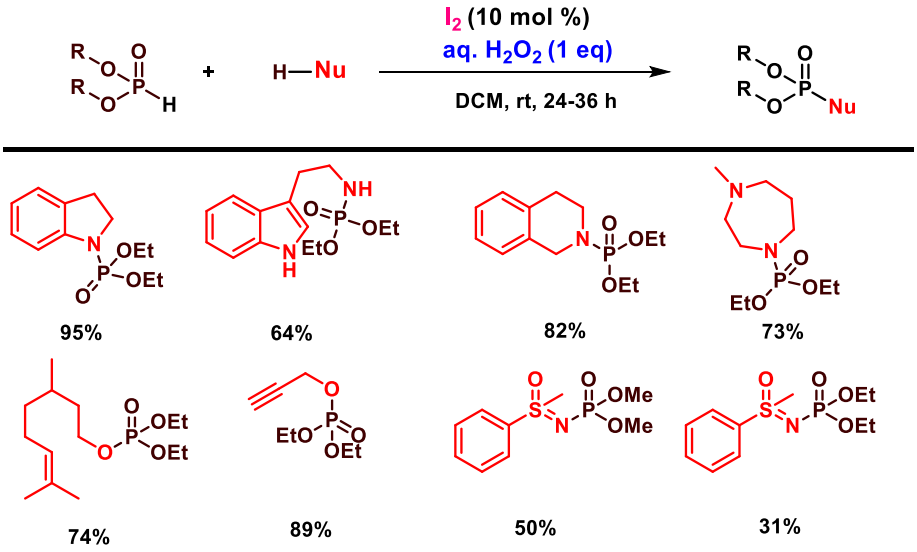
Scheme 1: A CDC coupling of tetrahydroisoquinoline with variety of nucleophiles

Chapter 2 describes the Cross Hetero Dehydrogenative Coupling (CHDC) reactions of amines, alcohols and sulfoximines with various phosphites.[4] Phosphoramidates and phosphate esters are structural scaffolds that are present in a variety of biologically active molecules.[5] The conventional methods for synthesizing phosphoramidates/phosphate esters largely involve treating alcohol/amine with appropriate phosphorus halides which generates stoichiometric amount of halogen waste.[6] Due to the usage of stoichiometric reagents and difficulties associated with the reported methods, there is a need for developing a protocol which is catalytic and mild. Therefore, we developed a method which employs catalytic amount of iodine and aq. H_2O_2 as a sole oxidant under milder conditions. Using this methodology, variety of phosphoramidates, phosphorous triesters and sulfoximine derived

[4] Dhineshkumar, J; Prabhu, K. R. *Org. Lett.* **2013**, *15*, 6062.

[5] (a) Berridge, M. J.; Irvine, R. F. *Nature* **1989**, *341*, 197. (b) Berridge, M. J.; Irvine, R. F. *Nature* **1984**, *312*, 315.

[6] Kosolapoff, G.M.; Maier, L. *Organic Phosphorus Compounds*; Wiley-Interscience: New York, 1972.



Scheme 2: Phosphorylation of amines, alcohols and sulfoximines

phosphoramidates have been synthesized with great efficiency and environmentally benign conditions. A few representative examples are highlighted in Scheme 2.[4]

Section B

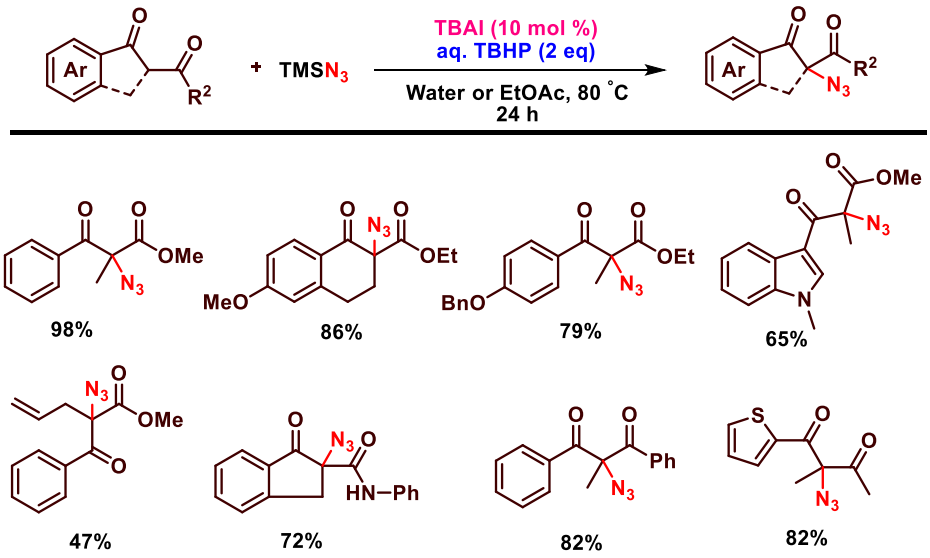
Chapter 1 of Section B demonstrates a mild way of synthesizing quaternary azides from α-substituted active methylene compounds which will serve as surrogates for several unnatural amino acid derivatives.[7] Azidation has emerged as one of the efficient methods to introduce nitrogen atom in to the organic molecules.[8] Azides are versatile functional groups which can be converted to amine, amide, and nitro compounds by simple modification. Moreover, azides are potential handle for "click" chemistry and provide late stage modifications in drug candidates, biomolecules and polymers, etc.[9] Azidation of 1,3-dicarbonyl compounds is challenging, as both azides and 1,3-dicarbonyl compounds are nucleophilic in nature. In this section of the thesis, azidation of 1,3-dicarbonyl compounds has been carried out using tetrabutyl ammonium iodide (TBAI) as a catalyst, aq. TBHP as an oxidant and $TMSN_3$ as a azide source. This method uses water as a solvent under mild reaction conditions to generate

[7] Dhineshkumar, J; Prabhu, K. R. *Eur. J. Org. Chem.* **2016**, *3*, 447.

[8] Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.*, **2005**, *44*, 5188.

[9] Sletten, E. M.; Bertozzi, C. R. *Acc. Chem. Res*. **2011**, *44*, 666.

quaternary azides in good to excellent yields. This operationally simple, practical, mild and green method provides an opportunity for synthesizing a variety of azidated β-keto esters, amides and ketones in good yields, Scheme 3.[7] The application of this methodology has been demonstrated by synthesising a few triazole and pyrazolone derivatives.

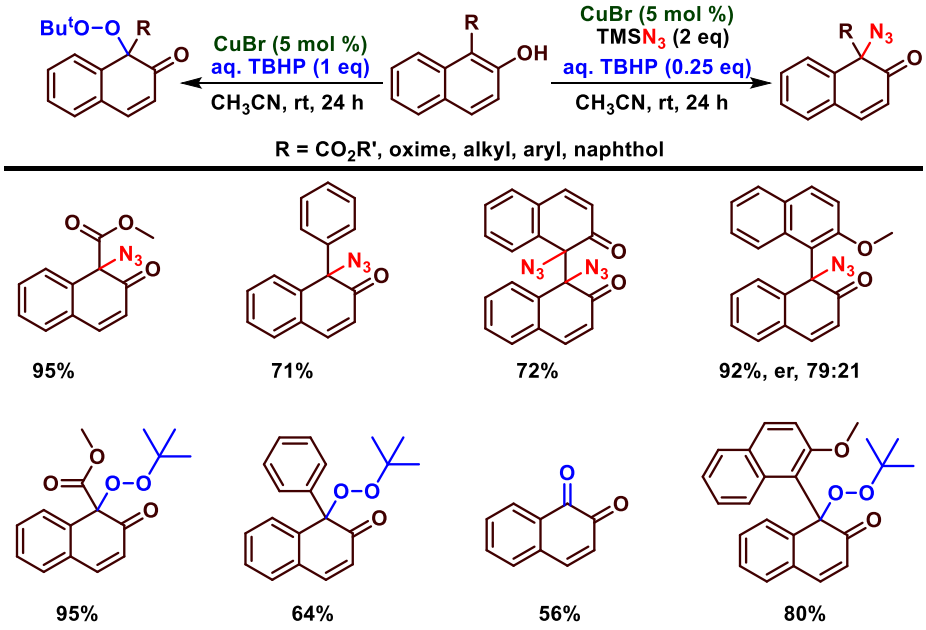


Scheme 3: Azidation of 1,3-dicarbonyl compounds

Chapter 2 of Section B comprises the azidation and peroxidation of β-napthol derivatives using dearomatization strategy. Azidation and peroxidation are efficient ways to introduce nitrogen and oxygen into organic molecules, which serve as surrogates for amines and alcohol functional groups. In the present study, the azidative or peroxidative dearomatization of naphthol derivatives have been described. The azidation of β-napthol derivatives has been achieved by using CuBr (5 mol %) as a catalyst, $TMSN_3$ as an azide source and aq. TBHP as an oxidant. Whereas, the peroxidation β-napthol derivatives has been accomplished using CuBr (5 mol %) in the presence of aq. TBHP at ambient reaction conditions.[10] The products obtained are naphthalenone derivatives, which serve as valuable

[10] Dhineshkumar, J; Samaddar, P; Prabhu, K. R. *Manuscript under revision.*

synthetic intermediates and has potential handle for further functionalization.[11] Several α-amino or α-peroxy naphthalenones are synthesized using this method in good yields. The usefulness of the methodology has been illustrated by synthesizing a few chiral azides and peroxides in good yields and with moderate enantioselectivity Scheme 4.[10]



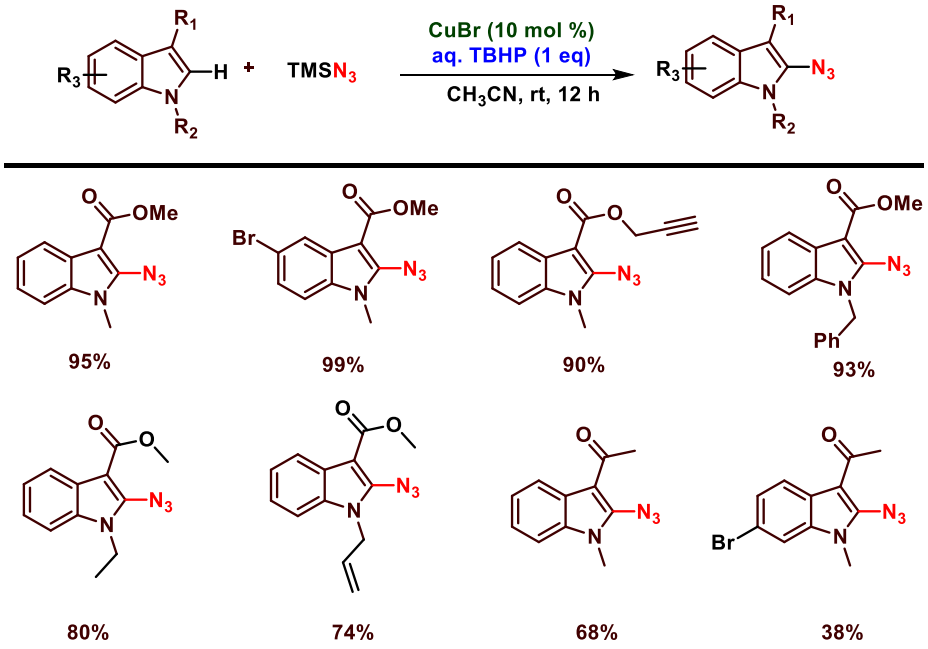
Scheme 4: Dearomatizative azidation and peroxidation of 2-naphthols

Chapter 3 reveals the azidation of indole at C-2 position by employing CuBr (10 mol %) as a catalyst and aq. TBHP as an oxidant in acetonitrile under reflux conditions (Scheme 5).[12] The C-H functionalization of indole at C-2 position is one of pivotal methods, since it paves a way for synthesizing a variety of indolo-alkaloids.[13] Azide is a versatile functionality which can be converted to several other nitrogen containing functional groups such as

[11] (a) Harris, W. M.; Geissman, T. A. *J. Org. Chem.* **1965**, 30, 432. (b) Valot, F. B.; Leboeuf, M.; Bouquet, A.; Cav, A. *Ann. Pharm. Fr*. **1977**, *35*, 65.

[12] Dhineshkumar, J; Karthik, G; Prabhu, K. R. *Manuscript submitted.*

[13] (a) Julian, P. L.; Meyer, E. W.; Printy, H. C. in Heterocyclic Compounds; Elderfield, R. C, Ed.; Wiley: New York, 1952; Vol. 3, pp 1-274. (b) Sundberg, R. J. The Chemistry of Indoles; Academic Press: New York, 1970.



Scheme 5: Azidation of indoles

amine, amide, triazole, etc.[9] A variety of functional groups were tolerated under the reaction conditions, and furnished the azidated product in good to excellent yields. Through radical inhibition study, we presume that the reaction may be proceeding through radical mechanism. In Scheme 5, a few representative examples are depicted.